admission by Applicants or Applicants' attorneys that such claims are not patentable, and Applicants reserve the right to prosecute such claims in a continuing application.

Claims 1, 3, 5, 6, 8, 10, 11, 13, 15-17, 19, and 21-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rhee, et al.

Claims 1, 2, 4, 6, 7, 9, 11, 12, 14, 16, 18, and 20 stand rejected under 35 U.S.C. 102(e) as being anticipated by Peterson, et al.

These rejections are respectfully traversed.

The present invention is directed to regenerating meniscal tissue in a joint of an animal, and to repairing meniscal damage of a joint, by injecting into the joint a liquid suspension comprising mesenchymal stem cells and an acceptable pharmaceutical carrier.

The present invention also is directed to repairing meniscal damage in a joint, reducing subchondral bone sclerosis in a joint, preventing or reducing the formation of osteophytes in a joint, and protecting cartilage in a joint of an animal, by injecting into the joint a liquid suspension comprising mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby the mesenchymal stem cells differentiate into meniscal tissue.

A liquid suspension is a preparation of cells dispersed in a liquid while retaining the physical properties of the liquid. Mesenchymal stem cells previously have been delivered to joints as part of a solid cell-matrix construct. References which disclose such delivery of mesenchymal stem cells accompany this Amendment and are listed in an accompanying Information Disclosure Statement. A solid cell-matrix construct usually consists of cells loaded onto a three-dimensional scaffold. A liquid suspension can be delivered to the joint by injection or catheter while a solid cell-matrix construct requires surgical delivery. Most cell-based therapies in which cells are delivered to a joint require opening of the joint capsule to implant the

cells. In Applicants' claimed methods, the surgery is not required and the joint capsule need not be opened. Instead, the liquid suspension containing the mesenchymal stem cells may be delivered by intraarticular injection. Such delivery is less traumatic and more efficient than surgery, and can be performed in an office setting.

With respect to the references cited by the Examiner, such cited prior art is directed to the use of mesenchymal stem cells, or bone and cartilage precursor cells, to produce new bone or new cartilage, or to the use of mesenchymal stem cells which are fibroblastic, to produce collagen where new connective tissue is needed.

None of the cited prior art, however, is directed to injecting mesenchymal stem cells into a joint in order to regenerate meniscal tissue in a joint or repair meniscal damage in a joint. Although the cited prior art states that mesenchymal stem cells may be used to produce new articular cartilage material, meniscal tissue has a number of features that distinguish it from articular cartilage.

Meniscus and articular cartilage have different compositions, structures, and mechanical functions. For example, the major macromolecule in the meniscus is Type I collagen, which has two $\alpha 1$ chains and one α 2 chain (See Adams, et al., <u>Knee Meniscus: Basic and Clinical Foundations</u>, Chapter 2, pages 15-28, Raven Press, Ltd., New York, 1992, a copy of which accompanies this Amendment), while the major component of articular cartilage is Type II collagen, which has three $\alpha 1$ chains. The collagen content of articular cartilage is about 60% of the dry tissue weight (Mankin, et al., <u>Osteoarthritis, Diagnosis and Medical/Surgical Management</u>, Chapter 5, Moskowitz et al., eds., Philadelphia, W. B. Saunders Company (1992), pages 109-154, at pg. 111), while meniscus has a collagen content up to 75% of its dry tissue weight (See Adams, et al., pg. 17, column 2, line 27). The proteoglycan content of the meniscus

is only about one-eighth of that in articular cartilage. (See Adams, et al. pg. 22, column 2, lines 9-11)

In addition, articular cartilage is divided into superficial, intermediate, and deep zones, and the collagen fiber orientations and proteoglycan contents vary in each zone. In the meniscus, the collagen fibers predominantly are in a circumferential arrangement, and they act as reinforcement for the meniscus to resist tensile stresses. (See Adams, et al., pgs. 19 and 20)

Also, the stiffness of the meniscus along the collagen fibers (i.e., in the circumferential direction) is one to two orders of magnitude higher than that of articular cartilage. (See Setton, et al., Clinical Orthopaedics and Related Research, number 367S, pgs. S254-S272, Lippincott, Williams & Wilkins, 1999, a copy of which accompanies this amendment). This high stiffness along the collagen fibers enables the meniscus to resist large circumferential stresses that arise when it is loaded. The resistance to fluid (i.e. permeability) of the meniscus is about one-sixth of that of articular cartilage, so that the meniscus resists fluid exudation to a greater extent than cartilage.(See Setton, et al., pg. S258, column 2 and pg. S259, column 1). The low permeability of the meniscus allows the meniscus to remain pressurized for long time periods after loading, so the meniscus acts as a fluid-filled cushion. Because meniscus and articular cartilage have different compositions, structures, and mechanical functions, the cited prior art, which discloses the use of mesenchymal stem cells or cartilage precursor cells, to produce cartilage such as articular cartilage, provides no basis for one of ordinary skill in the art to provide Applicants' claimed methods of regenerating meniscal tissue and repairing meniscal damage in a joint.

Rhee discloses crosslinked polymer compositions which may contain biologically active agents or cells, including mesenchymal stem cells. The compositions, as indicated at Column 18, lines 45-59, may be used as a replacement material for synovial fluid in osteoarthritic joints

by restoring a soft hydrogel network in a joint, or they also can be used as a replacement material for the nucleus pulposus of a damaged intervertebral disk.

At Column 16, lines 5-17, Rhee states that examples of mesenchymal stem cells include osteoblasts, chondrocytes, and fibroblasts, and that the polymer compositions may be used to deliver osteoblasts to the site of a bone defect to produce new bone, to deliver chondrocytes to the site of a cartilage defect to produce new cartilage, or to deliver fibroblasts to produce collagen wherever new connective tissue is needed.

Rhee, however, does not disclose or even remotely suggest to one of ordinary skill in the art that the polymer composition, which may contain mesenchymal stem cells, may be used to repair meniscal damage or regenerate meniscal tissue in a joint. Rhee, therefore, does not anticipate Applicants' invention as claimed, nor does Rhee render Applicants' invention as claimed obvious to one of ordinary skill in the art.

Peterson discloses the isolation of bone and cartilage precursor cells from hematopoietic and non-hematopoietic cells. The precursor cells may be isolated from peripheral blood, marrow, or adipose tissue based on binding by a reagent to CD34 or to other surface antigens on CD34+ cells. The isolated CD34+ precursor cells, as indicated at Column 5, lines 20-41, can be transplanted *in vivo* for bone or cartilage regeneration. In the working examples, such isolated precursor cells are used to repair calvarial defects.

In contrast, in Applicants' invention as claimed, Applicants inject mesenchymal stem cells, which are not CD34+ cells, into a joint in order to regenerate meniscal tissue in the joint.

Thus, Peterson, by his own admission, does <u>not</u> use mesenchymal stem cells to regenerate meniscal tissue in a joint or repair meniscal damage in a joint.

In addition, although Peterson appears to imply at column 4, lines 4-18 that the cells isolated by Peterson may be used to regenerate cartilage, the cartilage which is referred to is articular cartilage. As hereinabove noted, however, articular cartilage is different from meniscus in terms of composition, structure, and mechanical function.

Peterson, therefore, clearly does not disclose or even remotely suggest to one of ordinary skill in the art that one may regenerate meniscal tissue in a joint or repair meniscal damage in a joint by injecting mesenchymal stem cells in conjunction with an acceptable pharmaceutical carrier. Peterson, therefore, does not anticipate Applicants' method as claimed, nor does Peterson render Applicants' method as claimed obvious to one of ordinary skill in the art.

Applicants were the first to discover that one could regenerate meniscal tissue in a joint, protect cartilage in a joint, reduce subchondral bone sclerosis, prevent or reduce the formation of osteophytes, and repair meniscal damage in a joint by injecting into the joint a liquid suspension comprising mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby the mesenchymal stem cells differentiate into meniscal tissue. The cited references, taken alone or in combination, do not even remotely suggest to one of ordinary skill in the art that mesenchymal stem cells can be injected into a joint, whereby the mesenchymal stem cells differentiate into meniscal tissue in order to regenerate meniscal tissue and/or repair meniscal tissue damage. Thus, the cited references do not anticipate Applicants' claimed method, nor do the cited references render Applicants' claimed method obvious to one of ordinary skill in the art.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections under 35 U.S.C. 102(b) and U.S.C. 102(e) be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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